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Adenosquamous Carcinoma Arising in a Mucinous Cystadenoma of the Pancreas

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Background: Approximately 500 cystic neoplasms of the pancreas have been reported, and among these the mucinous pancreatic cystadenomas are known to have malignant potential. We report a rare case of a mucinous cystadenoma containing adenosquamous carcinoma.
Methods: We studied the histochemical and immunohistochemical staining characteristics of the tumor by staining with hematoxylin/eosin, Alcian Blue/Periodic Acid Schiff, and with immunoperoxidase-labelled antibodies against carcinoembryonic antigen, epithelial membrane antigen, low and high molecular weight cytokeratins, the proliferation antigen Ki-67, and the tumor suppressor antigen p-53. The K-ras oncogene was analyzed by direct sequencing.
Results: This case illustrates the usual presentation and features of this unusual tumor—a middle aged woman with abdominal pain and no history of alcohol abuse or abdominal trauma. The mucinous cystic tumor of her pancreas was composed predominantly of benign epithelium with areas of a malignant component that were identified by thorough sampling.
Conclusion: We discuss the nomenclature of these neoplasms and suggest that continuing efforts to subclassify mucinous cystic pancreatic tumors histologically may not be necessary, since the tumors are all histologically similar and are malignant or have malignant potential, and for all, treatment should include resection. J. Surg. Oncol. 64:159–162

KEY WORDS: **cystic neoplasm; occult malignancy; immunohistochemistry; classification**

INTRODUCTION

Cystic pancreatic neoplasms (CPN) are heterogeneous and are still being characterized by investigators, and malignant CPN represent approximately only 1% of primary pancreatic malignant tumors [1]. Over the last two decades there has been considerable discussion in the literature regarding the classification of CPN, and most investigators agree that the serous tumors are essentially benign, whereas the mucinous tumors should be regarded as being malignant or as having malignant potential [2–6]. Mucinous CPN therefore should be treated by resection [4,5,7–11].

We report the case of a patient with a mucinous cystadenoma of the pancreas containing adenosquamous carcinoma and describe the tumor's histologic transition from benign metaplastic mucin-producing epithelium to dysplastic to invasive adenosquamous epithelium, including its characteristic mucin staining with Alcian Blue/Periodic Acid Schiff, and also describe the positive marking of cells with antibodies against the p-53 tumor

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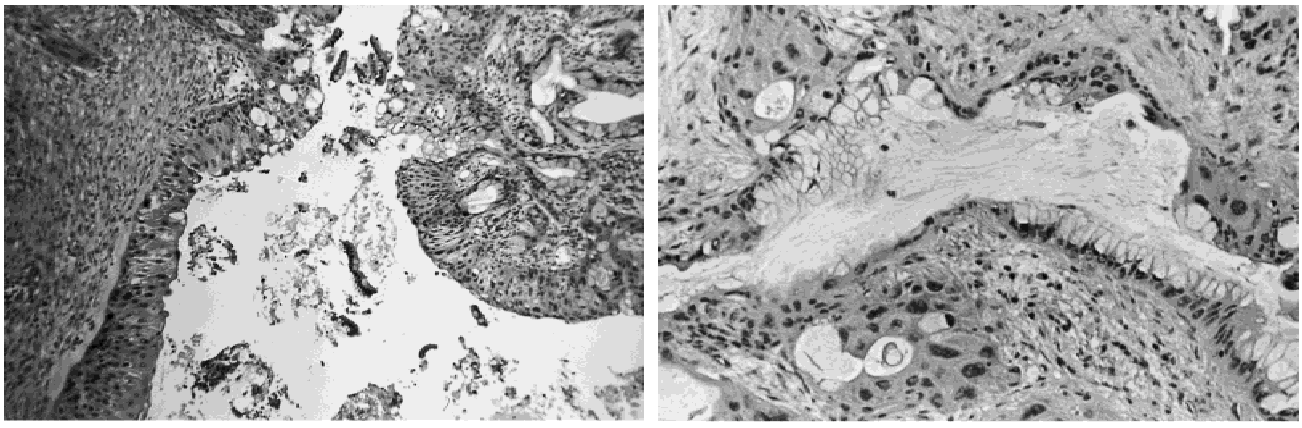

A B

Fig. 1. **A.** This case of adenosquamous carcinoma occurring in a mucinous cystadenoma is characterized in part by ectatic ductules lined by metaplastic, mucin-producing cells (top right), and dysplastic squamous epithelium (Hematoxalyn/Eosin, 60×). **B.** In some areas there is a transition between the metaplastic epithelium to invasive adenosquamous carcinoma. Note the intercellular bridging (bottom center) (Hematoxalyn/Eosin, 150×).

suppression antigen, proliferation antigen Ki-67, and K-ras point mutation.

We discuss the classification of cystic neoplasms of the pancreas and suggest that the earlier, relatively simple scheme of identifying these neoplasms as being serous or mucinous [1,5], rather than more recent attempts to subclassify the lesions by apparent histologic or anatomic origin, is sufficient characterization to result in appropriate surgical therapy.

CASE PRESENTATION

The patient is a 65-year-old, previously healthy, nondiabetic, Caucasian woman with a 32-pack-year history of cigarette use and a rare user of alcohol, who presented with a 2-month history of right upper quadrant pain radiating to her back. Pre-operative studies included an abdominal computerized axial tomography scan, which showed a 5 cm cystic and solid mass in the head of the pancreas. A celiac angiogram was performed and showed no evidence of vascular invasion. The patient's serum CA 19-9 level was >200 U/ml (reference range < 37 U/ml), and her CEA was 17 ng/ml (reference range < 5 ng/ml).

She underwent an uncomplicated subtotal pancreaticoduodenectomy. A cystic tumor of the pancreas was diagnosed as adenosquamous carcinoma arising in a mucinous cystadenoma (pathology discussed below). She had an uneventful early postoperative course, was discharged after 10 days, and was tolerating her diet well.

One month after the operation, the patient was readmitted for complaints of diarrhea, lower abdominal pain, and anorexia, and was explored for intra-abdominal abscesses that were not secondary to a pancreatic leak. She was discharged home 2 weeks later without complication.

PATHOLOGY

The first intraoperative frozen section biopsies of tissue taken from the head of the pancreas showed chronic pancreatitis and fragments of fibrotic pancreatic tissue with areas of mucinous metaplasia in the larger pancreatic ducts. The main resection specimen comprised a 35.5 cm segment of small bowel to which was attached a portion of the pancreas measuring 7.5 × 5.4 × 2.5 cm. An unremarkable gallbladder was also examined. The pancreas was firm and contained a 2.2 cm cyst, adjacent to a 2.5 cm firm gray-tan mass. Frozen section diagnosis of the mass was carcinoma. Frozen sections of pancreatic and common bile duct margins were negative for in situ or invasive carcinoma.

Permanent sections confirmed the frozen section diagnoses of both carcinoma and fibrotic pancreas with ducts and ductules lined by benign mucin-producing columnar cells. There was duct ectasia. On routinely processed (formalin-fixed, paraffin-embedded, and hematoxylin/eosin-stained) sections of the m ass that was seen grossly, there were proliferating invasive anaplastic ductal structures. Some of the ducts were lined or partially lined by large cells with varying amounts of eosinophilic cytoplasm and large nuclei with nucleoli and stippled and clumped chromatin patterns (Fig. 1A,B). There were invasive nests composed of malignant mucin-producing cells and squamous epithelium with intracellular bridging (Fig. 2). Most of the malignant glandular cells and glandular lumens stained violet with Alcian Blue/Periodic Acid-Schiff.

Immunoperoxidase-labelled antibody stains were performed. The malignant cells decorated with carcinoembryonic antigen, epithelial membrane antigen, and both low and high molecular weight cytokeratins. The p-53 stain decorated the nuclei of both the adenosquamous

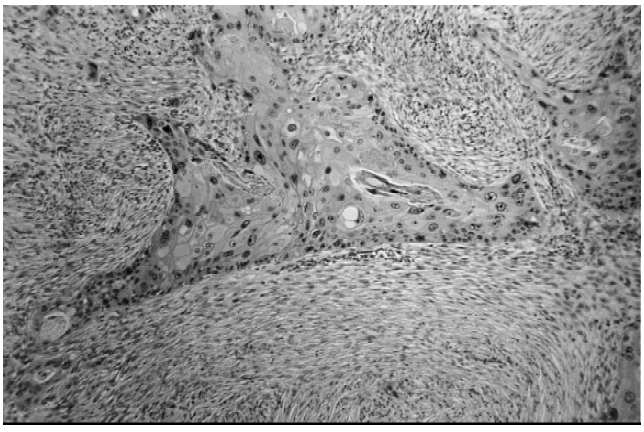

Fig. 2. This carcinoma contained invasive nests of pleomorphic cells with keratinization and formation of small lumina (Hematoxalyn/Eosin, 60×).

cells and the metaplastic mucin-producing cells; marking <15% of the metaplastic cells, progressing to >85% of the frankly malignant cells, and elucidating a transition to malignancy. The Ki-67 stained predominantly the adenosquamous cells, marking some basal cells in the malignant transition area, with scattered positive cells in the invasive neoplasm (23% of cells marking). A K-ras point mutation was detected by DNA sequencing. The mutation was a G to C transversion in the first position of codon 12, which would result in the substitution of arginine for glycine.

Two of 19 lymph nodes contained metastatic adenosquamous carcinoma.

DISCUSSION

Approximately 500 cases of CPN have been reported. Most cystic lesions of the pancreas are pseudocysts; neoplastic, retention, and congenital cysts accounting for the remainder of cases [2,11–13]. Perhaps only 9–10% of cystic pancreatic lesions are neoplastic [1,3,5,6,11,14] and these tumors represent only 1% of primary pancreatic malignancies [1].

The patient we present had a mucinous cystadenoma containing adenosquamous carcinoma. Her clinical presentation was typical for patients with CPN—a middle aged (or older) woman with abdominal pain and no history of alcohol abuse or of trauma.

Histologically there was a transition from benign metaplastic mucin-producing ductal epithelium to dysplastic, to invasive adenosquamous epithelium, with areas that clearly contained no malignancy. It is for this reason that such a lesion must be thoroughly sampled for diagnosis, as areas of malignant transformation can exist in largely benign lesions [2,4–7,9,14]. Fine-needle aspiration biopsies, therefore, with their small sample size, could easily provide a false negative result in this type of lesion.

When stained with Alcian Blue/Periodic Acid Schiff, the tumor was seen to contain violet-staining sialomucin. This is typical for malignant mucinous pancreatic tumors, whereas normal pancreatic tissue and benign pancreatic lesions more often contain neutral or sulfomucin [5,6,8,10,15,16]. Like the AB/PAS, the p-53 staining we observed is also helpful in biopsy diagnosis, because it is known to be positive in many malignant pancreatic tumors, and generally negative in benign lesions [17,18]. The Ki-67 stain, a marker of cell proliferation expressed in the nucleus of cycling cells, has been correlated with tumor aggressiveness and is thus considered a prognostic factor [19–21]. A K-ras mutation, as detected in this specimen, occurs in 70–90% of pancreatic ductal adenocarcinomas and is a sensitive marker for pancreatic carcinoma [22]. Because mutations also have been detected in ductectatic-type mucinous cystadenomas as well as hyperplastic lesions associated with chronic pancreatitis, however, K-ras point mutations cannot be considered specific for pancreatic malignancy [23,24].

Over the last two decades there has been considerable discussion in the literature regarding the classification of cystic pancreatic neoplasms [1–18,25]. There have been attempts to divide the mucinous CPN into various categories or subgroups (other than cystadenoma and cystadenocarcinoma), including a duct-ectatic variant, main and branch duct variants, papillary-cystic, and side branch variants [7,8,15,16,25]. These authors point out that although there are differences between these ''types'' based on the demographics of the small numbers of patients that they studied, the lesions are histologically indistinguishable, all appear to originate from ductal epithelium, and behave in the same way. The majority of investigators agree that the serous tumors are essentially benign and that the mucinous tumors should be regarded as being malignant or as having malignant potential [2,3,5,6,8[and have good responses with resection, and because of this, all mucinous CPN (regardless of their subclassification) should be treated by resection [4,5,7–11].

The mucinous cystic pancreatic neoplasms are unusual tumors with varied histologies, and as this case illustrates, can contain malignancies. They are known to have malignant potential even when overt malignancy is not identified on biopsy or sampled by the pathologist on resection. Because of this and patients' good prognosis with surgical resection, mucinous cystic neoplasms of the pancreas should be regarded by the surgeon as resectable lesions.

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